

Pseudoguaianolides: Recent Advances in Synthesis and Applications

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Pseudoguaianolides belong to the class of sesquiterpene lactones and are characterized by the lactone ring *cis* or *trans*-annellated (in 6,7- or 7,8- position) to fused seven- and five-membered rings; they differ from guaianolides for the position of the methyl group in 5. The unusual tricyclic fused core 5/7/5 was a challenge and inspired new synthetic methodologies to install substituents with proper stereochemistry. Despite their potential of application in different fields, their exploitation is so far very limited. Because of this, with this review we wanted to give perspectives in terms of availability and resupply of the most active compounds of the class.

Keywords: Sesquiterpene lactones, Pseudoguaianolides, Exo-methylene, Michael addition.

Pseudoguaianolides belong to the class of sesquiterpene lactones, one of the most abundant class of natural products [1]. More than 8000 structures have been reported, and they have broad structural and functional diversity[2]. All natural sesquiterpene lactones show a 15-carbon core structure (hence the prefix sesqui-) which is derived from the assembling of three isoprene units and a γ -lactone ring. They are characterized by a rather scattered botanical distribution, but they occur chiefly in the Asteraceae [3, 4]. The lactone component is characterized by an exo-methylene fragment thought to be responsible for the majority of biological activities induced by sesquiterpene lactones when administered to organisms or cells. Sesquiterpene lactones are primarily classified on the basis of their carbocyclic skeletons into germacranolides, which represent the largest subgroup and contain a 10-membered ring, eudesmanolides which are bicyclic 6/6 compounds, guaianolides (including *seco*-guaianolides and featuring a 5/7 bicyclic core), and pseudoguaianolides (Figure 1).

The exocyclic α,β -unsaturated carbonyl structures react by a Michael-type addition with nucleophiles in biological systems, such as the sulfhydryl group of the amino acid cysteine. By testing sesquiterpene lactones in cell-based assays, however, it has been found that some have very specific effects, and possibly specific targets. With their 5/7/5 skeleton, guaianolides and pseudoguaianolides represent the most common structure. Whilst guaianolides have been excellently recently reviewed by Macias and al. [5, 6], in this paper we intend to give an overview on the most updated synthetic methodologies in the synthesis of pseudoguaianolides, whilst their natural occurrence, possible ecological role and biological activities have been already reviewed [7, 8].

PSEUDOGUAIANOLIDES

Pseudoguaianolides are characterized by the lactone ring *cis* or *trans*-annellated (in 6,7- or 7,8- positions, Figure 1) to fused seven- and five-membered rings; they differ from guaianolides for the position of the methyl group in 5. Pseudoguaianolides include the less abundant helenanolides group in which the methyl in C-10 is α - on the *trans*-hydroazulene nucleus (Table 1, i.e. helenalin, mexicanin, aromatin) and the more abundant ambrosanolides group (with 10 β -methyl configuration; i.e. confertin, parthenin, damsine, ambrosin); in both the methyl configuration in C-7 is β . Pseudoguaianolides show several strong biological activities; in this paper, we reviewed the syntheses of compounds with known cytotoxic or antitumor activity, as listed in Table 1.

The basic synthetic strategies of guaianolides differ in the construction of the hydroazulene skeleton. The most used approach consisted in the addition of a cycloheptene ring to an oxidated cyclopentane. Other strategies utilized the transannular cyclizations of a proper cyclodecane or the rearrangement of a hydronaphthalene precursor. Final stages of the syntheses are the careful construction of the γ -butyrolactone and its α -methylenation.

Helenalin (1). Total syntheses of the racemic linear pseudoguaianolide **helenalin (1)** have been reported by Grieco[9, 10] and Schlessinger [11]. In the former approach, Grieco demonstrated that the intermediate **11**, already used for the synthesis of ambrosanolides damsine and ambrosin (6,7-annulated pseudoguaianolides), could be as much usefully employed in the synthesis of helenanolides, which differ for the α or β configuration of the methyl in C10. The norbornadiene derived cyclopentenol **11**

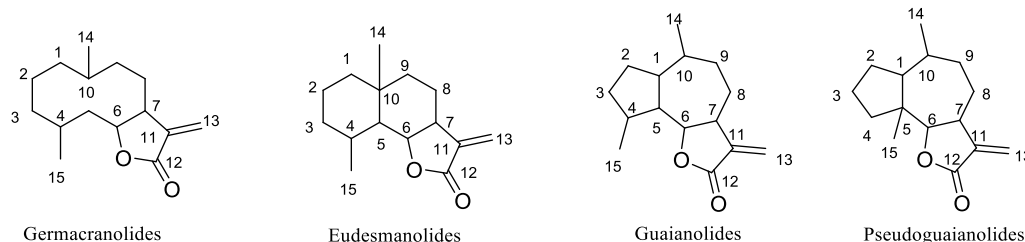
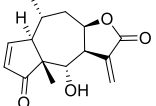
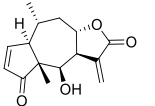
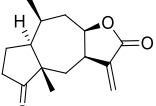
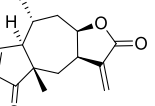
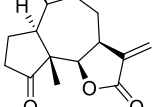
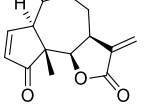
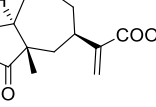
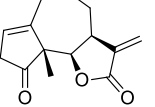
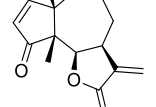
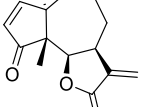
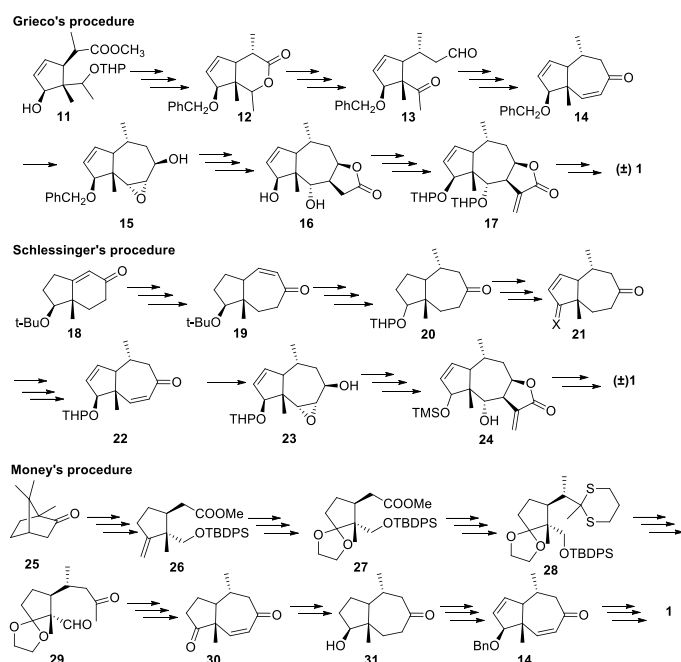


Figure 1: Structure and numbering of the main classes of sesquiterpene lactones.

Table 1: List of pseudoguaianolides, their first isolation and biological activity.

Compound / First isolation / Cytotoxicity	Compound / First isolation / Cytotoxicity
 Helenalin (1) <i>Helenium microcephalum</i> [12] Alkylating bifunctional agent which induces: 1. direct modification of the p65 subunit of NF- κ B, leading to molecule inactivation. 2. thiol depletion 3. induction of apoptosis [2, 13-15] Genotoxic [14]	 Mexicanin I (2) <i>Helenium mexicanum</i> [16] Cytotoxic towards the human KB cervix carcinoma cell line; it inhibits c-Myb target genes expression in human leukemia cell line and human leukemia cells proliferation [17].
 Confertin (3) <i>Ambrosia confertiflora</i> [18] Significant cytotoxic activity against a panel of six human tumor cell lines [19]	 Aromatin (4) <i>Helenium aromaticum</i> [20] Aromatase inhibitor. Cytotoxic against KB cell line [21]
 Damsin (5) <i>Ambrosia maritima</i> [22] Significant cytotoxic activity against a panel of human tumor cell lines [19, 23] Candidate to treat refractory tumors [24]	 Ambrosin (6) <i>Ambrosia maritima</i> [22] Cytotoxic inducing apoptosis in Jurkat leukemia T cells and against a panel of human tumor cell line [23, 25]
 Damsinic acid (7) <i>Ambrosia ambrosioides</i> [26] Cytotoxic [27]	 Neoambrosin (8) <i>Hymenoclea salsola</i> [28] Cytotoxic and candidate to treat refractory tumors [24]
 Hymenin (9) <i>Hymenoclea salsola</i> [29] Cytotoxic inducing apoptosis in Jurkat leukemia T cells [30]	 Parthenin (10) <i>Parthenium hysterophorus</i> [31] Cytotoxic against several human cancer cell lines [32-34]

**Scheme 1:** Syntheses of helenalin (1).

was converted into the hydroazulenone **14** through several steps of protection and deprotection, lactonization with complete

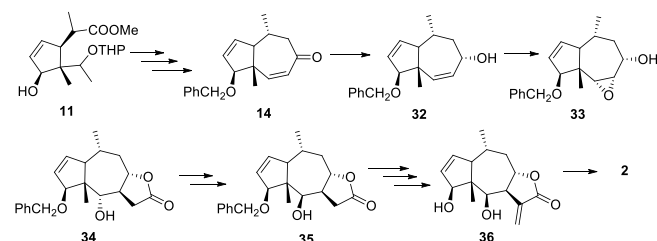
isomerization of the C10 methyl group (**12**), reduction to the corresponding lactol converted into the ketoaldehyde **13**, intramolecular aldol condensation, final multi-step conversion of the protected aldol (Scheme 1). Diastereoselective epoxidation (with hindered *t*-butylhydroperoxide) and quantitative and exclusive stereospecific reduction gave the epoxyalcohol **15**, which was treated with excess dilithioacetate in order to introduce the necessary two carbon chain in C7 along with epoxide opening. The following step of debenzilation however would require the noxious protection step of the lactone ring. This was avoided by directly adding the intermediate trianion to a solution of lithium in liquid ammonia, followed by acidic aqueous workup; this procedure enabled the direct conversion of **15** into the tricyclic debenzylated lactone **16**. α -Methylenation was performed on the lactone bis(tetrahydropyranyl) ether via hydroxymethylation, mesylation, and elimination to give intermediate **17**; deprotection and final oxidation gave (\pm)-helenalin [9].

In the latter synthetic approach, Schlessinger proposed the same precursor hydroazulenone **19** for the synthesis of (\pm)-helenalin as for confertin and damsine [11]. The intermediate **19**, prepared from the readily available enone **18**, was converted into the 10-methyl analogue **20** by using methylmagnesium bromide, that underwent ketal protection and oxidation. The cyclopentenone ring in **21** ($X=O$) was obtained by alkylation with a disulfide, followed by oxidation and sulfoxide elimination; it was then converted into **21** ($X=OTHP$, H) through intermediate steps of reduction and alcohol protection. The cycloheptenone ring in **22** (THP analogue of **14**)

was obtained via deprotonation and treatment of the intermediate silylenol ether with palladium acetate. Then diastereoselective epoxidation and ketone reduction gave α -epoxy alcohol **23**. Subsequent epoxide ring opening using excess dilithioacetate, acid-catalysed lactonization, and eventually methylenation afforded protected dihydrohelenalin **24**; deprotection and oxidation gave pure racemic helenalin in 6.6% yield from enone **18**.

Formal racemic and enantioselective syntheses of helenalin have been described later [35-37]. In the Money's enantioselective version [37], key intermediate was the ketal ester **27** derived from camphor (**25**), which showed to be useful in the synthesis of both helenanolides and ambrosanolides. Steps of the synthesis were the stereoselective methylation of the above ketal ester, reduction to alcohol, conversion into iodide and then to ketal dithiane **28**. After ketal hydrolysis, TBDPS deprotection and Swern oxidation gave keto aldehyde **29**, which upon intramolecular aldol condensation was converted into enedione **30**. Regio- and stereoselective reduction and catalytic hydrogenation gave hydroxy ketone **31** which was finally converted in enantiomerically pure enone **14** previously used in helenalin synthesis (Scheme 1, Grieco's synthesis) [10].

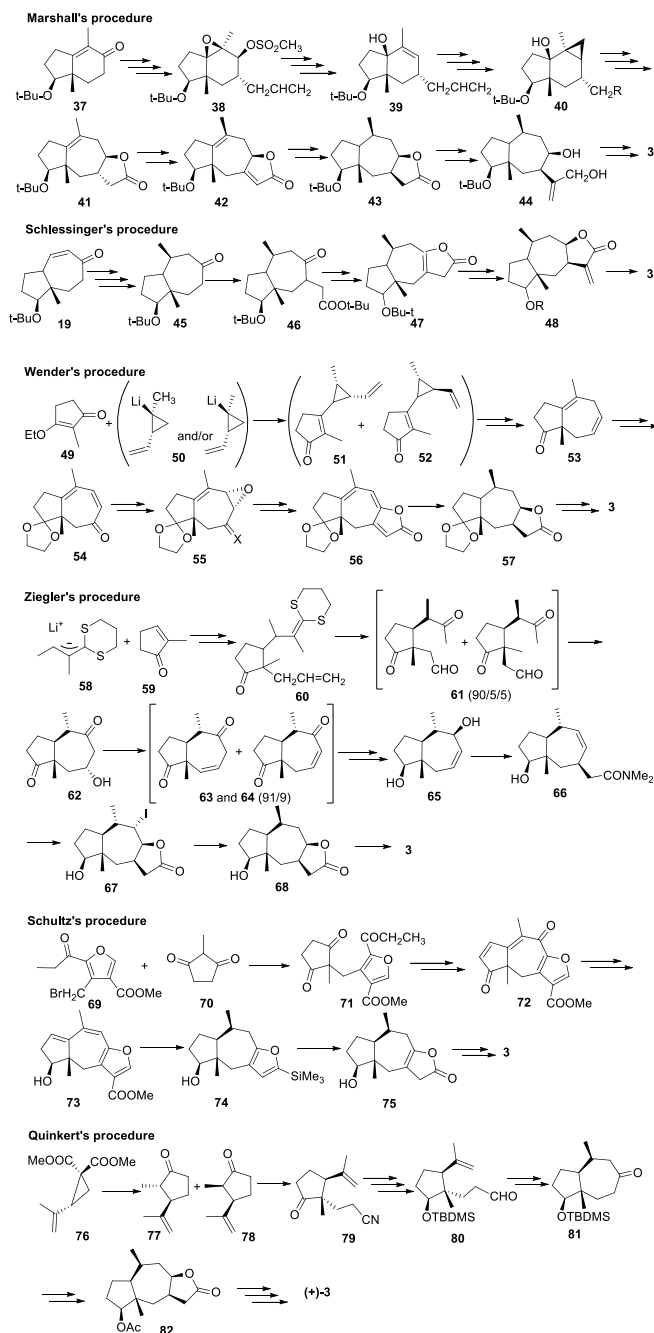
Mexicanin I (2). Structurally related to helenalin, **mexicanin I** features opposite configuration in C6 and C8, therefore their syntheses were reported at the same time. In 1983 Grieco described stereocontrolled mexicanin I synthesis as described in Scheme 1 for helenalin, by using as starting reagent the same cyclopentenol **11** until hydroazulenone **14** (Scheme 2) [38]. In order to obtain proper configuration, the reaction sequence required a first reduction to alcohol **32** and then diastereoselective epoxidation to epoxyalcohol **33**. Treatment with metalated acetic acid gave the tricyclic lactone **34**. The inversion of configuration at C6 was achieved through consecutive oxidation/ reduction that, in the presence of the bulky angular methyl in C5 occurred at the α face (**35**). The completion of the synthesis required a modified procedure with respect to that of helenalin. In order to maintain the *trans*-fused tricyclic lactone in C7-C8, protection of the C(6) hydroxyl group as tetrahydropyranyl ether was requested. The subsequent three-step sequence of α -methylenation and deprotection led to tricyclic lactone **36**, that underwent final oxidation to (\pm)-mexicanin I (**2**; Scheme 2).



Scheme 2: Grieco's synthesis of mexicanin I (**2**).

Confertin (3). The previously mentioned Money's enantioselective approach for helenalin was applied also in the formal synthesis of mexicanin I from camphor derived dienone **14** as well as in that of confertin [37]. After the first stereoselective total synthesis of (\pm)-confertin (**3**) reported in 1976 [39], several other procedures were reported [39-50], which often include the synthesis of the C10 epimer (\pm)-aromat and of the 6,7-annulated lactone damsine and damsine acid. Total syntheses of (+)-confertin date from 1987 [51-54].

In 1976 Marshall constructed hydroazulene skeleton starting from the keto ether **37** (Scheme 3) derived from 2-methyl-1,3-cyclopentanedione [39]. Key steps of α -allylation, ketone reduction,



Scheme 3: Syntheses of confertin (**3**).

epoxidation and lithium-ammonia reduction of mesylated derivative **38** gave alcohol **39**, which underwent Simmons-Smith cyclopropanation to cyclopropylcarbinol **40** ($R=CHCH_2$) with well-defined stereochemistry. Ozonolysis and treatment with silver oxide afforded acid **40** ($R=COOH$) which stereospecifically rearranged to the hydroazulene lactone **41** with the uncorrected configurations of the lactone ring. Conversion into the *cis*-lactone **43** was obtained through treatment with diphenyl diselenide and lithium diisopropylamide followed by hydrogen peroxide to **42** and then catalytic hydrogenation to **43**. α -Methylenation required the use of 11-carbomethoxy derivative of lactone **43**, enolate formation and reduction to the diol **44**. Oxidation of the primary alcohol, cyclization into the desired α -methylene- γ -butyrolactone, *t*-butyl ether cleavage and final oxidation of the resulting alcohol gave (\pm)-confertin (**3**).

The Schlessinger protocol relies on the hydroazulenone **19**, key intermediate for the synthesis of (±)-helenalin [11, 42]. The first step was the methylation to afford β-methyl derivative **45** which was converted into (±)-confertin and (±)-damsin. In the first case, the enolate of cycloheptanone **45** was reacted with *t*-butyl iodoacetate (**46**), which in turn was converted into its corresponding enol lactone **47** and then reduced. The final α-methylenation of the protected lactone and oxidation of the deprotected secondary alcohol (**48**) gave confertin (30% overall yield from **19** over 12 steps).

In Wender's procedure, (±)-confertin was synthesized along with (±)-damsinic acid from the cycloheptadienone **53** [43], relying on the same methodology previously described for divinylcyclopropane preparation, which effected the requisite pseudoguaiane annulation. The mixture of the two divinylcyclopropanes **51** and **52** was subjected to repeated cycles of photoepimerization and pyrolysis to give exclusively ketone **53**; this was converted into its ketal and then almost chemoselectively oxidized to the common precursor **54**. Further steps involved epoxidation, olefination to *E* and *Z* esters **55** (X=CHCOOEt), whose treatment with acid gave hydroxylactones and, upon base treatment, triene lactones **56**. Catalytic hydrogenation of **56** gave final lactone **57** further converted in (±)-confertin **3**; the overall yield was 5-10% (12 steps).

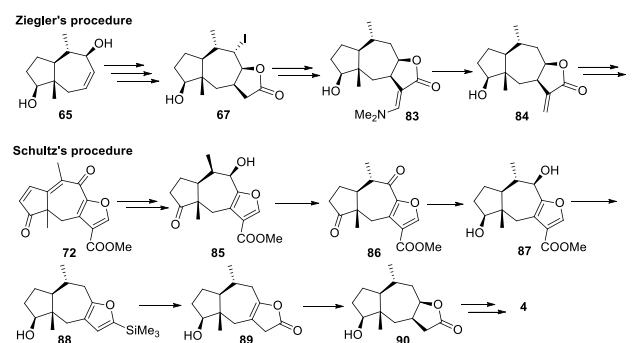
Heathcock reported a new route for pseudoguaianolide synthesis which employed hydronaphthalene compounds as precursor of the hydroazulene skeleton [45]. The complex synthesis furnished (±)-confertin in 2.7% overall yield, and additionally accomplished the formal synthesis of (±)-helenalin. A different approach was proposed by Semmelhack: in this case a low yield of (±)-confertin was obtained by hydrogenation of the pseudoguaiane tricyclic skeleton obtained via a Ni-promoted intramolecular coupling of a sulfonium intermediate giving rise to cyclization-lactonization [41]. In the frame of Michael addition of vinylogous dithiane (dithianylidene) anions investigations, Ziegler and Fang reported a new methodology for the synthesis of (±)-confertin (**3**) and (±)-aromatin (**4**) [44, 47, 55, 56]. The lithium anion **58**, easily available from 2-ethylidene-1,3-dithiane, was reacted with 2-methylcyclopentenone (**59**) and allylated to give a mixture of three diastereomers **6**. These ones when subjected to ozonolysis gave a mixtures of tricarbonyl compounds (**61**). Base treatment afforded the single aldol **62**, whose dehydration with methanesulfonic acid/P₂O₅ gave a mixture of enones **63** and **64**; reduction and chromatographic purification finally gave diol **65** which bears the required stereochemistry at C1, C5 and C10. The introduction of acetic acid chain in C7 was achieved using the Eschenmoser variant of Claisen rearrangement furnishing amide alcohol **66**; subsequent steps were the formation of iodide *cis*-lactone **67**, dehydroalogenation and diastereoselective catalytic hydrogenation (**68**); final oxidation and α-methylenation gave confertin **3**.

A new strategy to pseudoguaianolides was proposed by Schultz for total syntheses of (±)-confertin and (±)-aromatin on a multigram scale [46, 48]. This synthetic approach was based on an annulation strategy that attempted to incorporate the α-methylene-γ-butyrolactone feature within the annulation reagent and allowed a formal total synthesis of confertin in a 22% overall yield from the annulation product **72**, this one prepared as reported in Scheme 3. The annulation reagent was prepared starting from the readily available furan ester **69** and 2-methylcyclopentane-1,3-dione (**70**); dehydrogenation and cyclodehydration gave enetrione **72**, which was converted, through several steps, into the final lactone **75** (intermediate also in both the Schlessinger and Heathcock syntheses of confertin).

Total synthesis of pure (+)-confertin has been reported by Quinkert [51, 53]. The enantiomerically pure dicarboxylate **76**, accessible via diastereoselective Linstead cyclopropanation, was converted by stereospecific ring expansion into cyclopentanones **77** and **78**, which through intermolecular Michael addition to acrylonitrile gave the *trans* adduct **79** as the only product. Following steps of synthesis were intramolecular hetero-ene reaction, oxidation and hydrogenation to give ketone **81**. Regioselective alkylation in C-7 and successive steps following Schlessinger procedure to **82** [42] gave pure (+)-confertin.

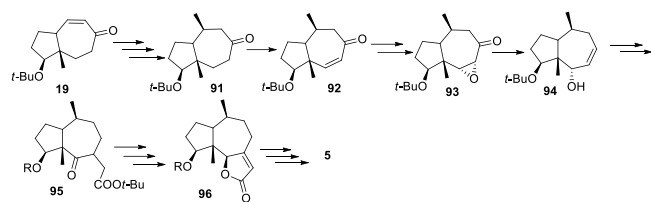
In 1992 Quinkert published an improvement in the enantioselectivity of this synthesis; the starting cyclopentanones **77** and **78** were prepared via enantioselective conjugate addition of a chirally modified organocuprate to 2-methylcyclopent-2-enone [54]. Finally, a formal enantioselective synthesis of (+)-confertin was reported by Shishido in 1998 in which the key step was a highly diastereoselective acyl radical-mediated cyclization [57].

Aromatin (4). Ziegler's procedure for confertin was applied also for (±)-aromatin (**4**) synthesis (Scheme 4) [44]. As previously described, the key intermediate *cis*-diol **65** was converted into the *cis*-iodolactone **67**; deiodination, methylenation with Bredereck's reagent to **83** and then reduction gave α-methylene-γ-butyrolactone **84**. Alcohol oxidation afforded dihydroaromatin, which was converted in aromatin via selenylation and selenoxide elimination. The seven-membered ring annulation strategy of Schultz was successfully applied in the synthesis of (±)-aromatin (**4**) [48]. The hydroxylactone **90**, was prepared from the annulation product **72** through several steps of reduction and oxidation (leading to ketoalcohol **85**, diketone **86** and diol species **87**), where epimerization occurred at C10 into the more stable α-configuration of the methyl group. Then hydrogenolysis, saponification, decarboxylation and reaction with *n*-butyllithium gave the TMS-derivative **88**. peroxyacid oxidation of **88** and catalytic hydrogenation gave intermediate **89**.



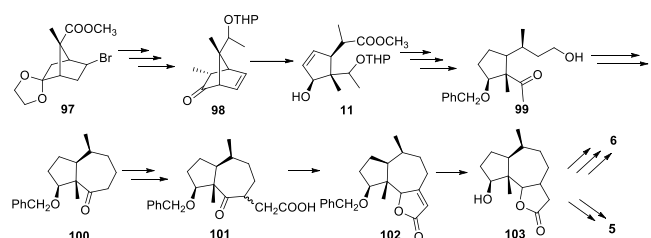
Scheme 4: Syntheses of aromatin (**4**).

Damsin (5), Ambrosin (6). The Schlessinger synthesis of (±)-damsin (**5**) was based on the hydroazulenone **19** (Scheme 5), the same key intermediate for the synthesis of (±)-helenalin and (±)-confertin, where transposition of the carbonyl residue from C8 to C6 is needed [11, 42]. After methylation to the β-methyl derivative **91**, the subsequent reaction steps included dehydrogenation on an intermediate enolsilane to give cycloheptenone **92**, stereoselective epoxidation to **93** and conversion into the allylic alcohol **94**, catalytic hydrogenation, alcohol oxidation and alkylation with *t*-butyl iodoacetate to give keto ester **95**. Formation of the enol lactone **96**, catalytic reduction, alcohol deprotection and final oxidation furnished damsin in an overall yield of 20% in 15 steps.



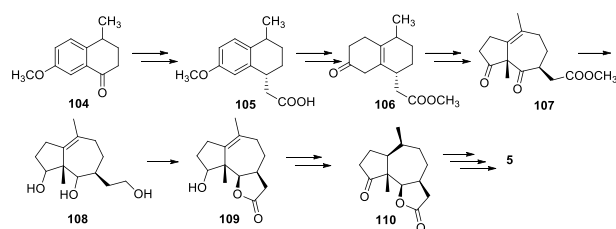
Scheme 5: Schlessinger's synthesis of damsine (5)

(±)-Damsine (5) and (±)-ambrosine (6) have been synthesized by Grieco [58]. The cyclopentenol derivative **11** (common reagent in Grieco helenalin synthesis, which bears correct configurations at C1, C5, and C10) was prepared from the norbornadiene derived ketal ester **97** through several synthetic steps. The perhydroazulenedione scaffold **100** was then constructed via reduction, benzylation, chain elongation, iodide conversion, intramolecular alkylation. Then it was converted first into ketoacid **101** through three steps (alkylation, ozonolysis, Jones oxidation), then butenolide **102**, and finally 4-hydroxyl γ -lactone **103** (after debenylation and reduction), which bears the correct five chiral centers of damsine. Damsine synthesis was completed by α -methylenation of the γ -butyrolactone ring and oxidation at C4. Ambrosine synthesis required introduction of an α -phenylselenenyl group in C-3 of damsine followed by its oxidative removal.



Scheme 6: Grieco's synthesis of damsine (5) and ambrosine (6)

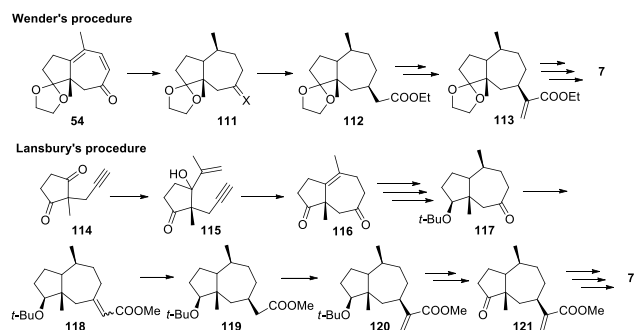
We have already abovementioned damsine syntheses described by Schlessinger [42], Grieco [58] and Money [37]. In a different approach Kretschmer started from the tetralone derivative **104**; reaction sequence afforded unsaturated ketone **106**, ozonolysis followed by a reductive work-up and methylation gave azulenedione **107** (via chromatography separation from its diastereomer) [59]. Ketone and acid reductions gave the triol intermediate **108**, which underwent oxidation to hydroxylactone **109**, catalytic hydrogenation and Jones oxidation to **110**, and final α -methylenation sequence to give damsine (5).



Scheme 7: Kretschmer's synthesis of damsine.

Almanza in 2015 described ambrosine semisynthesis from damsine, available in good amounts from *Ambrosia arborescens* [60]. (±)-Ambrosine was obtained by Saegusa-Ito oxidation of a silylenol ether derivative of damsine in better yields than the above Grieco procedure.

Damsinic Acid (7). Following the aforementioned Wender's protocol [43], **damsinic acid (7)** was prepared in a 20% overall yield over 11 steps. Ketal ketone **52** was stereoselectively reduced

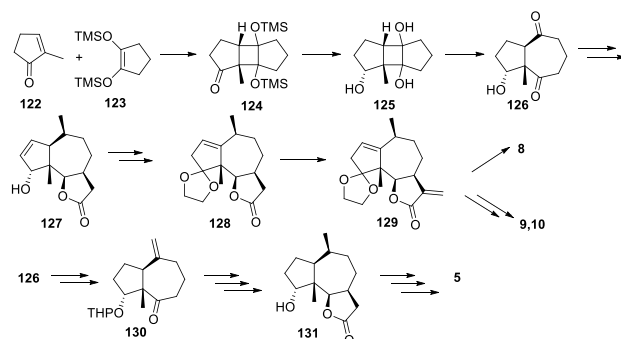


Scheme 8: Synthesis of damsinic acid (7).

to ketone **111** (X=O), then converted into ester **111** (X=CHCOOEt) which was hydrogenated to ester **112** with 90% stereoselectivity; final standard methylenation afforded **113** and then (±)-damsinic acid (7).

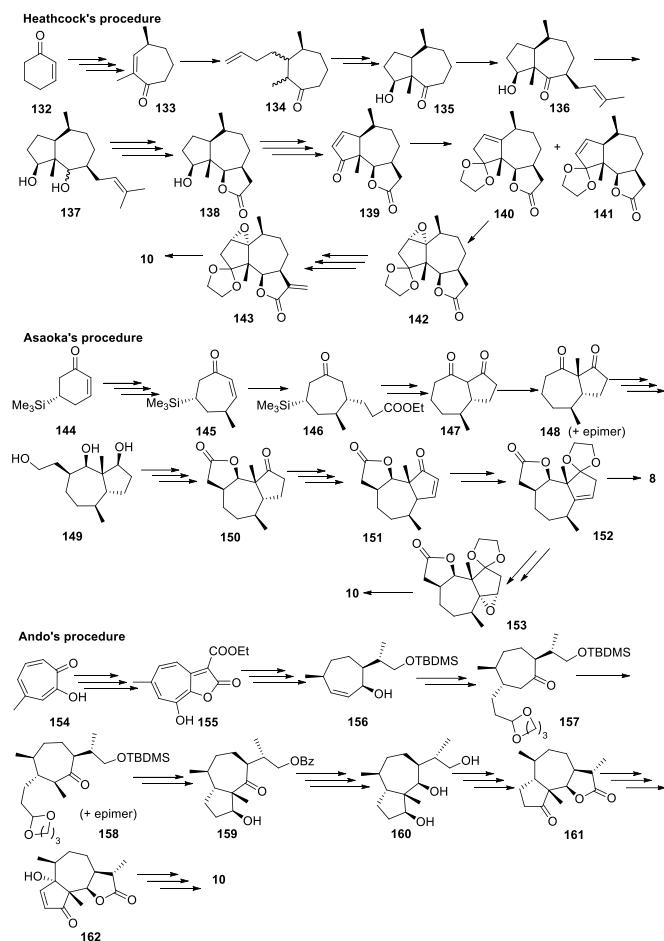
Total synthesis of damsinic acid has been reported by Lansbury [61]. In the Lansbury procedure, hydroazulenedione **116** was prepared from conversion of substituted cyclopentanedione **114** into **115** and then intramolecular cyclization to **116**; reduction (on a 7-thioketal intermediate) and hydrogenation to **117**, side chain introduction (**118**), hydrogenation again (**119**), α -methylenation (**120**), oxidation (**121**) and finally hydrolysis furnished damsinic acid. A formal synthesis of damsinic acid was also reported by Kawahara [62].

Neoambrosine (8), hymenin (9), parthenin (10). Vandewalle reported the first total synthesis of racemic **damsine (5)**, **neoambrosine (8)**, **hymenin (9)** and **parthenin (10)** [63]. The key intermediate of the synthetic neoambrosine was obtained via intermolecular [2+2] photocycloaddition of 1,2-bis(trimethylsilyloxy)cyclopentene (**123**) and 2-methyl-2-cyclopentenone (**122**) gave the photoproduct **124**; reduction and deprotection generated tricyclic triol **125**; cyclobutane ring cleavage furnished hydroxyketone **126**. The same intermediate, transformed into the lactone **127**, was used in the synthesis of the three above mentioned pseudo-guaianolides. Selenylation and selenoxide elimination gave the corresponding cyclopentenone derivative; migration of the double bond was achieved by acidic treatment on the ketal derivative (**128**), α -methylenation to **129** and finally ketal hydrolysis gave neoambrosine **8**. Epoxidation furnished two isomers; chromatographic separation afforded epoxide ring opening and β -elimination yielding directly racemic hymenin (**9**) and parthenin (**10**).



Scheme 9: Vandewalle's synthesis of neoambrosine, parthenin, hymenin and damsine.

After the first synthesis reported by Vandewalle (Scheme 9), few years later Heathcock reported a new multi-step procedure for (±)-parthenin [64]. The synthetic approach entailed first the synthesis of



Scheme 10: Syntheses of parthenin

the cycloheptane ring and then the fusion of the five membered ring following a method developed by the same authors. As reported in Scheme 10, cycloheptanone **133** (easily obtained from cyclohexenone **132**) was converted into diastereomeric mixture of adduct **134** by using Yamamoto's reagent; annulation product **135** was then obtained via ozonolysis and acidic treatment of the aldehyde intermediate. A subsequent five-step procedure enabled an efficient and enantioselective construction of the γ -butyrolactone ring of **138** on a gram-scale by choosing proper alkylating and protecting groups. After alcohol oxidation, silyl enol ether formation and direct oxidation to enone **139**, enone ketalization afforded a diastereomeric mixture of **140** and **141**. Single epoxidation of **140** afforded **142** with the desired configurations at C1 and C2; α -methylation of the lactone ring (as Schlessinger's work, Scheme 1) and final acidic treatment of **143** gave racemic parthenin (22 steps from **134**, 0.25% overall yield).

An enantioselective synthesis of parthenin and neoambrosin from optically pure **144** was described by Asaoka [65]. The stereocontrol strategy took advantage from the presence of the trimethylsilyl

group on the unsaturated seven membered ring. Adduct **145** was obtained by stereoselective introduction of methyl group to give a silyl enol ether intermediate, cyclopropanation and dehydrochlorination. 1,4-Addition gave a diastereomeric mixture of **146**; by reacting pure (–)-**146**, pure desilylated lactone **147** was obtained. Methylation gave **148** in epimeric mixture; pure (–)-**148** was converted in a multi-step reaction into the triol **149**, which was oxidized first to lactone and then to ketolactone **150**. Silylation and oxidation gave **151**, followed by protection and migration of the double bond to **152**. α -Methylation and deacetalization of **152** gave neoambrosin (**8**), whilst Heathcock's procedure through epoxide **153** afforded parthenin (**10**).

Few years later, total synthesis of (\pm)-**10** was described by Ando [66]. The key intermediate **156**, prepared from 4-methyltropone (**154**) through intermediacy of **155**. Upon oxidation and Grignard reagent addition from the α -face the resulting enone **157** was obtained, whose methylation gave **158**. The benzoate ester of **158** was then subjected to acid-catalyzed intramolecular aldol condensation (**159**). Reduction afforded triol **160**; air oxidation of the primary alcohol, lactonization and oxidation of the secondary alcohol furnished ketolactone **161**. Several steps were required in order to stereoselectively introduce the γ -hydroxy- α,β -unsaturated ketone, involving protection/deprotection steps, dehydrogenation, epoxidation and hydrolysis; the final intermediate α -methyl- γ -lactone hymenolin **162** was converted into the α -methylene- γ -lactone parthenin through α -bromination and then dehydrobromination.

Conclusions

Sesquiterpene lactones represent a large and vastly important group of compounds. A number of compounds belonging to this class have been shown to be active in terms of bioactive agents combating human disease, the most known are for example parthenolide and helenalin. It seems almost certain that, even though the reasons of efficacy cannot be generalized too broadly, the effects can often be ascribed to the presence of functional groups specific to the class, typically the characterizing α -methyl- γ -lactone group, or extra-ring unsaturated carbonyl moiety. Among the sesquiterpene lactones, pseudoguaianolides represent an interesting class of targets. In this review, we collected the most recent syntheses of the pseudoguaianolide core. The unusual tricyclic fused core 5/7/5 was a challenge and inspired new synthetic methodologies to install substituents with proper stereochemistry. The most of the references relied on synthesis rather than semi-syntheses, implying that the stereochemistry is installed correctly by the exploitation of mainly diastereoselective reactions. Pseudoguaianolides, guaianolides and more in general sesquiterpene lactones as a whole represent a large and vastly important group of compounds, with high potentiality for biomedical applications. Despite this, their exploitation is so far very limited. Because of this, with this review we wanted to give perspectives in terms of availability and resupply of the most active compounds of the class.

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